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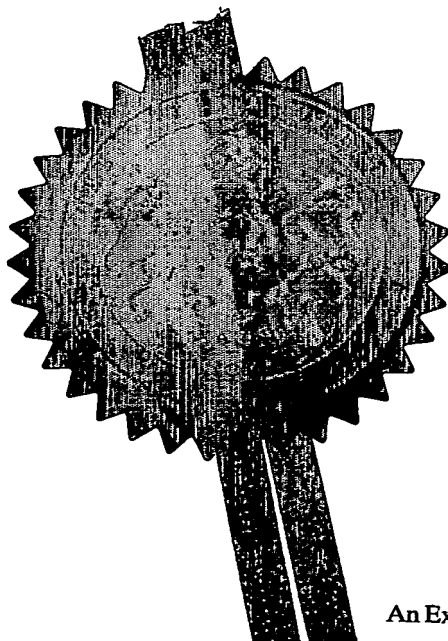
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*P. Mahoney*

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Dated 17 April 2003

15 OCT 2002

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1/77

16 OCT 02 E753869-7 D00524  
P01 700 0-00 0223977.0

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1.	Your reference	G-32503P1/ABR 9922		
2.	Patent application number (The Patent Office will fill in this part)	0223977.0		15 OCT 2002
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	BIOCHEMIE GBESELLSCHAFT MBH A-6250 KUNDL TIROL AUSTRIA 8355158001		
	Patent ADP number (if you know it)			
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA		
4.	Title of invention	Organic compounds		
5.	Name of your agent (if you have one)			
	"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
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	a) any applicant named in part 3 is not an inventor, or			
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## Patents Form 1/77

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Description 8

Claim(s) 2

Abstract 1

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

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Request for substantive examination (*Patents Form 10/77*)

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11.

I/We request the grant of a patent on the basis of this application

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Date

B. A. Yorke & Co.

B.A. Yorke & Co.

15 October 2002

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Mrs. E. Cheetham  
020 8560 5847

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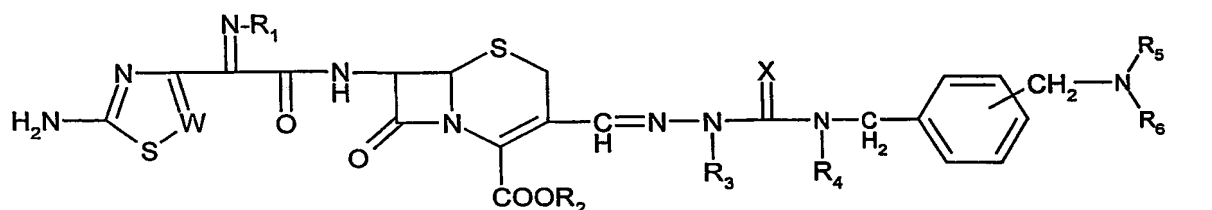
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**Organic compounds**

The present invention relates to organic compounds e.g. antimicrobial compounds such as cephalosporins.

- 5 In one aspect the present invention provides a compound of formula



wherein

W is CH or N,

R<sub>1</sub> is hydrogen or O-R<sub>1</sub>,

- 10 R<sub>1</sub> is hydrogen, (C<sub>1-6</sub>)alkyl, halo(C<sub>1-6</sub>)alkyl or hydroxycarbonyl(C<sub>1-6</sub>)alkyl,

R<sub>2</sub> is hydrogen or an ester moiety,

R<sub>3</sub> is hydrogen, (C<sub>1-2</sub>)alkyl, allyl or (C<sub>3-8</sub>)cycloalkyl,

R<sub>4</sub> is hydrogen or (C<sub>1-2</sub>)alkyl,

R<sub>5</sub> and R<sub>6</sub> independently of each other are hydrogen, (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkyl-carbonyloxy,

- 15 arylcarbonyloxy, (C<sub>1-6</sub>)alkylsulfonyl or arylsulfonyl, and

X = NH, O or S.

CH<sub>2</sub>NR<sub>5</sub>R<sub>6</sub> can be in o, m or p position.

- In a preferred aspect the present invention provides a compound of formula I wherein R<sub>1</sub> is  
 20 hydroxy or fluoromethoxy, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen, R<sub>3</sub> is methyl and the group  
 CH<sub>2</sub>NR<sub>5</sub>R<sub>6</sub> group is in p position.

An ester moiety includes alkyl; e.g. unsubstituted alkyl or substituted alkyl, e.g. by

aryl, such as benzyl, alkoxybenzyl, such as 4-methoxybenzyl, alkoxy, such as

- 25 methoxymethyl; alkyloxycarbonyloxy; alkyl; alkoxy, such as glycyloxy, phenylglycyloxy, e.g.  
 glycyloxymethyl, phenylglycyloxymethyl; heterocyclyl e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl;  
 indanyl, phthalidyl, alkoxy carbonyloxy and ester moieties which form with the COO<sup>-</sup> group a  
 physiologically hydrolysable and acceptable ester, e.g. such known to be hydrolysable ester  
 groups in the field of cephalosporins. A compound of formula I may thus be in the form of an

physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and - acceptable esters as used herein is meant an ester in which the COO- group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

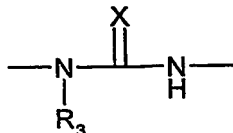
10 If not otherwise indicated herein any carbon containing group may contain up to 20 carbon atoms. Aryl includes (C<sub>6-18</sub>)aryl, preferably phenyl, naphthyl, e.g. phenyl.

Any group(s) may be unsubstituted or one or morefold substituted, e.g. by groups as conventional in cephalosporin chemistry.

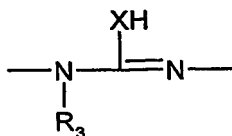
15 In this specification unless otherwise indicated terms such as "compound of formula I" embrace the compound in any form, for example in the form of a salt and in free base form. The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, 20 quaternary salt and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts, preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. The amino group of the 25 cyclohexyl ring in a compound of formula I may be e.g. a  $\text{NH}_3^+$  group,  $\text{NR}_5\text{R}_6\text{R}_7^+$ ,  $\text{NHR}_5\text{R}_6$  or  $\text{NH}_2\text{R}_5$ , wherein  $\text{R}_5$  and  $\text{R}_6$  have the before said meanings and  $\text{R}_7$  independently of  $\text{R}_5$  and  $\text{R}_6$  may have the same meaning as those. Counterions are those as conventional, e.g. hydroxy or chloride ions. A free form of a compound of formula I may be converted into a salt form, a solvate form or a salt and a solvate form and *vice versa*.

30 In a further aspect the present invention provides a compound of formula I in the form of a salt, for example an acid addition salt or a metal salt, e.g. and a compound of formula I in free form, in the form of a salt, in the form of a solvate or in the form of a salt and a solvate.

The present invention includes a compound of formula I in any isomeric/tautomeric form in which it may exist. E.g. the configuration in group



may (co)exist in the form of

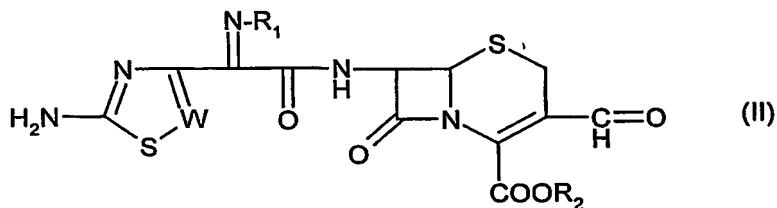


Also e.g. geometric isomers if R<sub>1</sub> is other than hydrogen may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I and corresponding stereoisomeric forms of a compound of formula I may be obtained, e.g. a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated according to a method of conventional.

The present invention includes a compound of formula I in any tautomeric form, in any isomeric mixtures and in the form of pure isomers.

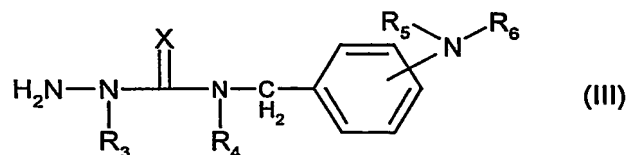
Any compound mentioned herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. analogously to a method as conventional or as disclosed herein.

In another aspect the present invention provides a process for the production of a compound of formula I by reacting a compound of formula



wherein R<sub>1</sub> and R<sub>2</sub> are defined as described before, with a compound of formula

- 4 -



wherein  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  are defined as described before.

- If desired, reactive groups may be protected with protecting groups, which may be, or, which are split off under the reaction conditions, or after the reaction. A compound of formula I wherein  $R_2$  is hydrogen may be converted into a compound of formula I wherein  $R_2$  is an carboxylic acid ester group. A compound of formula I may be isolated from the reaction mixture as appropriate, e.g. analogously to a method as conventional.
- 10 The compounds of formula I including salt/solvate, hereinafter designated as "active compound(s) of the invention" exhibit pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, e.g. antibacterial, activity against e.g. gram negative and gram positive bacteria, e.g. gram positive bacteria, such as e.g. *Escherichia*, e.g. *Escherichia coli*;
- 15 *Enterobacter*, e.g. *Enterobacter cloacae*; *Enterococcus*, e.g. *Enterococcus faecalis*; *Klebsiella*, e.g. *Klebsiella pneumoniae*; *Streptococcus*, e.g. *Streptococcus pneumoniae*; *Staphylococcus*, e.g. *Staphylococcus aureus*; and *Pseudomonas*, e.g. *Pseudomonas aeruginosa*, in vitro in the Agar Dilution Test according to National Committee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3Vol.13, No. 25: "Methods for dilution
- 20 Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition, Approved Standard". The active compounds show an MIC ( $\mu\text{g/ml}$ ) in the Agar Dilution Test from about  $<0.0125$  to ca.  $>6.25$ . The active compounds of the invention show a surprising overall activity spectrum. The activities for a salt form and/or a solvate form of the compound of formula I are in the same range as the activity of the compound of formula I in free form.
- 25 In another aspect the present invention provides an active compound for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.
- In a further aspect the present invention provides an active compound of the present invention for use in the preparation of a medicament for the treatment of microbial diseases,
- 30 for example diseases mediated by bacterias selected from *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Streptococcus*, *Staphylococcus* and *Pseudomonas*.
- The present invention provides in further aspects

- an active compound of the present invention for use as a pharmaceutical in the treatment of microbial diseases caused by bacterias selected from *Escherichia*, *Enterobacter*, *Enterococcus*, *Klebsiella*, *Streptococcus*, *Staphylococcus* and *Pseudomonas*; and
- the use of an active compound of the present invention or the use of a pharmaceutical composition comprising an active compound of the present invention as a pharmaceutical

In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.

10 Treatment includes disease treatment as well as prophylactic treatment.

For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I used, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day.

15 An active compound of the invention may be administered by any conventional route, for example orally, *e.g.* in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, *e.g.* in analogous manner to ceftazidime.

The compound of example 1 is a preferred compound of the present invention.

It has, for example been determined that the MIC ( $\mu\text{g/ml}$ ) of the compound of Example 1 against, for example *Klebsiella pneumoniae* is about 0.0125. It is therefore, indicated that for the treatment of microbial diseases, *e.g.* bacterial diseases, the preferred compounds of the invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally used with ceftazidime.

25 The compounds of formula I may be administered in pharmaceutically acceptable salt form, *e.g.* acid addition salt form or base addition salt form or in the corresponding free forms, optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

In another aspect the present invention provides a pharmaceutical composition comprising an active compound of the present invention in association with at least one



pharmaceutically excipient. Such compositions may be manufactured accordingly, e.g. analogously to a method as conventional. Pharmaceutical excipient(s) include(s) pharmaceutically active excipient.

- 5 In the following examples which illustrate the present invention all temperatures are given in degree centigrade. RT means room temperature.

**EXAMPLE 1****A) SYNTHESIS OF INTERMEDIATE COMPOUNDS****a) Benzylidene derivative of 3-amino-1-[3-(aminomethyl)benzylamino]-3-methyl-guanidine in the form of a monohydrochloride**

5 35 g of the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide in the form of a hydrochloride and 32.79 g of 3-aminomethylbenzol in 300 ml of MeOH are refluxed. The mixture obtained is stirred at RT, a precipitate forms, is filtered off and solvent is evaporated. The evaporation residue obtained is treated with 217.5 ml of 2M HCl, a precipitate formed is filtered off, washed and dried. The volume of the filtrate obtained is brought to about 150 ml, a precipitate is formed, filtered off, washed and dried. The dried, combined precipitates are recrystallized from water and the benzylidene derivative of 3-amino-1-[3-(aminomethyl)-

10 benzylamino]-3-methyl-guanidine in the form of a monohydrochloride is obtained.

**b) 3-amino-1-[3-(aminomethyl)benzylamino]-3-methyl-guanidine dihydrochloride**

From a mixture of 24.74 g of the benzylidene derivative of 3-amino-1-[3-(aminomethyl) benzylamino]-3-methyl-guanidine in the form of a monohydrochloride in 79.9 ml of 2M HCl, benzaldehyde is distilled off and solvent from the remaining mixture is evaporated. 3-amino-1-[3-(aminomethyl)-benzylamino]-3-methyl-guanidine is obtained in the form of a dihydrochloride.

15

**20 B) SYNTHESIS OF SUBSTITUTED CEPHALOSPORINES****a) 3-{{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-[[[(5-amino-[1,2,4]thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino]-3-cephem-4-carboxylic acid trihydrochloride**

To a mixture of 2 g of 3-[amino-1-(aminomethyl)benzylamino]-3-methyl-guanidine in the form of a dihydrochloride in 3.4 ml of 2M HCl and 6.1 ml dimethylacetamide, 2.78 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide are added and the suspension obtained is stirred at RT. The mixture obtained is poured into acetonitrile under stirring. A precipitate formed is filtrated off, washed and dried. 3-{{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-[[[(5-amino-[1,2,4]thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino]-3-cephem-4-carboxylic acid is obtained in the form of a trihydrochloride.

25

30

**b) 3-{{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-[[[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]**

**amino}-3-cephem-4-carboxylic acid monohydrochloride**

10 g of the crude 3- $\{(\text{E})[[1\text{-}[3\text{-(aminomethyl)benzylamino]iminomethyl}]\text{-methylhydrazono}]\text{methyl}\}$ -7- $\{[(5\text{-amino-1,2,4-thiadiazol-3-yl})\text{-(Z)-(fluoromethoxyimino)-acetyl}]\text{amino}\}$ -3-cephem-4-carboxylic acid in the form of a trihydrochloride are dissolved in 42 ml of water and subjected to chromatography (e.g. LiChroprep RP-18<sup>R</sup>, Merck, grain size 40-63  $\mu\text{m}$ ). Fractions containing the desired compound in the form of a monohydrochloride (HPLC determination) are combined and optionally lyophilised. 3- $\{(\text{E})[[1\text{-}[3\text{-(aminomethyl)benzylamino]iminomethyl}]\text{-methyl-hydrazono}]\text{methyl}\}$ -7- $\{[(5\text{-amino-1,2,4-thiadiazol-3-yl})\text{-(Z)-(fluoromethoxyimino)-acetyl}]\text{amino}\}$ -3-cephem-4-carboxylic acid is obtained in the form of a monohydrochloride, optionally as a lyophilizate.

***<sup>1</sup>H-NMR (200 MHz, DMSO-*d*<sub>6</sub>)***

3.41, s, 3H, NCH<sub>3</sub>; 3.52, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 3.88 – 4.12, m, 2H, NCH<sub>2</sub>; 4.40 – 4.80, m, 3H, 2H from NCH<sub>2</sub> and 1H from SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 7.22 – 7.58, m, 4H, aromatic H; 8.14, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

According to the method as described in Example 1, but using the appropriate starting materials the following compounds are obtained.

**Example 2:** Compound of formula I wherein R<sub>1</sub> is OCH<sub>2</sub>F, R<sub>3</sub> is CH<sub>3</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> are H and the CH<sub>2</sub>NR<sub>5</sub>R<sub>6</sub> group is in p position:

***<sup>1</sup>H-NMR (200 MHz, DMSO-*d*<sub>6</sub>)***

3.38, s, 3H, NCH<sub>3</sub>; 3.52, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 3.90 – 4.12, m, 2H, NCH<sub>2</sub>; 4.50 – 4.80, m, 3H, 2H from NCH<sub>2</sub> and 1H from SCH<sub>2</sub>; 5.28, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.78, d, J=55 Hz, 2H, CH<sub>2</sub>F; 5.96, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 7.28 – 7.60, m, 4H, aromatic H; 8.14, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH.

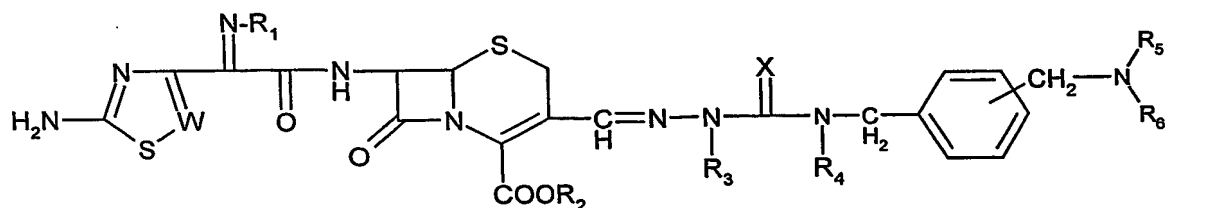
**Example 3:** Compound of formula I wherein R<sub>1</sub> is OH, R<sub>3</sub> is CH<sub>3</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> are H and the CH<sub>2</sub>NR<sub>5</sub>R<sub>6</sub> is in p position:

***<sup>1</sup>H-NMR (200 MHz, DMSO-*d*<sub>6</sub>)***

3.37, s, 3H, NCH<sub>3</sub>; 3.57, part of the AB-quartet, J=18 Hz, 1H, SCH<sub>2</sub>; 3.90 – 4.10, m, 2H, NCH<sub>2</sub>; 4.45 – 4.75, m, 3H, 2H from NCH<sub>2</sub> and 1H from SCH<sub>2</sub>; 5.15, d, J=5 Hz, 1H,  $\beta$ -lactam; 5.74, dd, J=5 Hz and 8 Hz, 1H,  $\beta$ -lactam; 6.88, s, 1H, CH thiazol; 7.20 – 7.55, m, 4H, aromatic H; 8.15, s, 1H, CH=N; 9.78, d, J=8 Hz, 1H, NH.

# Patent claims

1. A compound of formula



wherein

W is CH or N,

R<sub>1</sub> is hydrogen or O-R<sub>1</sub>'

R<sub>1</sub>' is hydrogen, (C<sub>1-6</sub>)alkyl, halo(C<sub>1-6</sub>)alkyl or hydroxycarbonyl(C<sub>1-6</sub>)alkyl,

R<sub>2</sub> is hydrogen or an ester moiety,

R<sub>3</sub> is hydrogen, (C<sub>1-2</sub>)alkyl, allyl or (C<sub>3-8</sub>)cycloalkyl,

R<sub>4</sub> is hydrogen or (C<sub>1-2</sub>)alkyl,

R<sub>5</sub> and R<sub>6</sub> independently of each other are hydrogen, (C<sub>1-6</sub>)alkyl, (C<sub>1-6</sub>)alkyl-carbonyloxy,

arylcabonyloxy, (C<sub>1-6</sub>)alkylsulfonyl or arylsulfonyl, and

X = NH, O or S.

2. A compound of formula I wherein R<sub>1</sub> is hydroxy or fluoromethoxy, R<sub>2</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are hydrogen, R<sub>3</sub> is methyl and the group CH<sub>2</sub>NR<sub>5</sub>R<sub>6</sub> group is in p position.

3. A compound according to claim 1 or 2 in the form of a salt.

4. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 in association with at least one pharmaceutical excipient.

5. A compound according to any one of claims 1 to 3 for use as a pharmaceutical.

6. A compound according to claim 5 for the treatment of microbial diseases.

7. A method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound according to any one of claims 1 and 4.

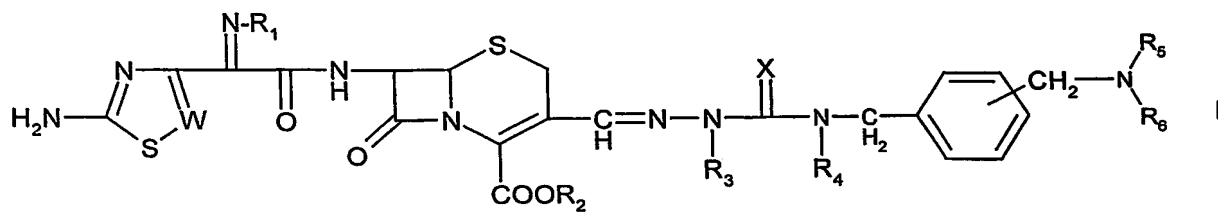
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IL/14-Oct-2002

**Abstract**

A compound of formula

5



wherein the substituents have various meanings, useful as a pharmaceutical.